REMARKS

The specification has been amended to recite the correct priority claim for the application. In particular, the specification has been amended to recite that the present application is a divisional application of U.S. Patent Application No. 09/385,219, filed on August 27, 1999, now U.S. Patent No. 6,720,181, which claims priority under 35 U.S.C. §119 to U.S. Provisional Patent Application No. 60/098,355, filed August 28, 1998, U.S. Provisional Patent Application No. 60/118,568, filed February 3, 1999, and U.S. Provisional Patent Application No. 60/124,449, filed March 15, 1999. The amendment to the specification does not constitute new matter.

Claims 50-74 were pending in the present application. Claims 56-74 have been withdrawn without prejudice as being drawn to non-elected subject matter. Applicants reserve the right to prosecute the withdrawn claims and subject matter in one or more related applications. Claims 75 and 76 have been added. Support for new claim 75 can be found in the specification at *e.g.*, Figure 8b and 8c. Support for new claim 76 can be found in the specification at *e.g.*, page 23, lines 25 to 29. Claims 51 and 52 have been amended to specifically point out and distinctly claim that which the Applicants regard as the invention. Specifically, claim 51 has been amended to recite, in part, an isolated nucleic acid molecule comprising a nucleotide sequence that is at least 25 consecutive nucleotides of SEQ ID NO: 9, which encodes an F-box polypeptide, or a fragment thereof. Support for the amendment to claim 51 can be found in the specification at *e.g.*, page 23, lines 1 to 14. Claim 52 has been amended to recite, in part, an isolated nucleic acid molecule that hybridizes under highly stringent conditions to the complement of nucleotide sequence of SEQ ID NO:9, and wherein said highly stringent conditions comprise hybridization in a buffer consisting of 0.5M $NaHP0_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA at 65°C, and washing in a buffer consisting of 0.1xSSC/0.1% SDS at 68°C. Support for the amendment to claim 52 can be found in the specification at *e.g.*, page 19, line 31 to page 20, line 7. Thus, no new matter has been added by these amendments.

Reconsideration and allowance of the present application in view of the remarks below are respectfully requested.

1. PRIORITY

The Examiner contends that the priority date of claims 51-55 is August 27, 1999, the filing date of U.S. Patent Application No. 09/385,219, now U.S. Patent No. 6,720,181, because SEQ ID NO: 9 of the instant application is not disclosed in U.S. Provisional Patent

Application No. 60/098,355, filed August 28, 1998, U.S. Provisional Patent Application No. 60/118,568, filed February 3, 1999, or U.S. Provisional Patent Application No. 60/124,449, filed March 15, 1999 ("the provisional applications"). Applicants submit that although the provisional applications do not disclose nucleotides 1410 to 2077 of SEQ ID NO: 9, the provisional applications do disclose nucleotides 1 to 1409 of SEQ ID NO: 9 (*see, e.g.*, the provisional applications at Figure 7A). Applicants respectfully point out that new claim 75, which relates to a nucleic acid molecule comprising a nucleotide sequence from nucleotide position 1 to nucleotide position 1409 of SEQ ID NO: 9, is fully supported by the provisional applications. As such, claim 75 has a priority date of August 28, 1998, which is the filing date of U.S. Provisional Patent Application No. 60/098,355.

2. REJECTIONS UNDER 35 U.S.C. § 101

The Examiner has maintained the rejection of claims 50-55 under 35 U.S.C. § 101 for lack of a specific and substantial asserted utility or a well established utility. Applicants respectfully disagree with the rejection for the reasons detailed below.

The Examiner requests that Applicants clarify the relationship between SEQ ID NO: 9, SEQ ID NO: 19, and FBP5 (see Office Action, page 7). The Examiner alleges that both SEQ ID NO: 19 and SEQ ID NO: 9 are identified as corresponding to FBP5 in the specification at page 8, line 3, and at page 9, lines 5-6, respectively. Applicants submit that SEQ ID NO: 19, which is referred to on page 8, line 3, corresponds to the amino acid sequence of the F-box motif of FBP5, which is a portion of FBP5, as recited in SEQ ID NO: 9. The description of Figure 1 states "Alignment of the conserved F-box motif amino acid residues in the human F-box proteins..." (see, the specification at page 8, lines 1 to 2). Applicants further submit that the specification clearly teaches that SEQ ID NO: 9 corresponds to the cDNA sequence of FBP5 (see, the specification at page 9, lines 6 to 7).

The Examiner contends that the basis for the utility rejection is that "the specification has failed to teach any functional characterization of the claimed nucleic acid or protein encoded thereby to support that it does have ubiquitin ligase function" (see, the Office Action, page 7). The Examiner questions "whether SEQ ID NO: 9 and sequences that hybridize to SEQ ID NO: 9 do encode a function ubiquitin ligase" (see, the Office Action, page 6). Applicants respectfully submit that the Examiner has applied an incorrect legal standard for satisfying 35 U.S.C. § 101. The standard for satisfying the utility requirement is

not whether the nucleic acid molecules of the present invention encode a functional ubiquitin ligase. The utility requirement under 35 U.S.C. § 101 does not equate to requiring that the nucleic acid molecules of the present invention have to encode a functional ubiquitin ligase.

To satisfy the requirements of 35 U.S.C. § 101, an applicant must claim an invention that is statutory subject matter and must show that the claimed invention is "useful" for some purpose explicitly or implicitly. *M.P.E.P. 2107.01.* Deficiencies under the "useful invention" requirement of 35 U.S.C. § 101 will arise when it is not apparent why the invention is "useful". *Id.* This can occur when applicant fails to identify any specific or substantial utility for the invention of fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. *Id.* citing *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966); *In re Fisher,* 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005); *In re Zeigler,* 992 F.2d 1197, 26 USPQ2d 1600 (Fed. Cir. 1993).

The Examiner points to the Revised Interim Utility Guidelines Training Materials ("the Guidelines") for definitions of "specific utility" and "substantial utility" (see Office Action, pages 5 to 6). According to the Guidelines, a specific utility is a utility that is specific to the subject matter claimed and a utility would not be considered to be specific in the absence of a disclosure of a specific DNA target (see Office Action, page 5). As discussed previously, the nucleic acid molecules of the present invention do have a specific DNA target, which encodes a novel ubiquitin ligase subunit F box protein 5 ("FBP5"), comprising an F-box motif. Thus, the nucleic acid molecules of the present invention do have a specific utility. Furthermore, the Guidelines state that a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. The specification discloses that F-box proteins, which are subunits of ubiquitin ligase, contain a motif, the F-box, that interacts with Skp1 (*see, e.g.,* the specification at page 2, lines 20 to 28). The specification also teaches that F-box proteins play a role in the ubiquitin pathway and the regulation of the G1 phase of the cell cycle. Therefore, F-box proteins may be useful for the treatment of proliferation and differentiative disorders (*see, e.g.,* the specification at page 58, lines 27 to page 59, line 36). Thus, unlike inventions that contain only a general statement of utility for unspecified diseases, the nucleic acid molecules of the present invention have a specific utility.

Furthermore, contrary to the Examiner's assertion that the only evidence provided in the specification that SEQ ID NO: 9 encodes a functional ubiquitin ligase is that SEQ ID

NO:10 shares homology to known ubiquitin ligases (*see*, the Office Action at page 6), Applicants respectfully point out that FBP5 was first identified based on its interaction with the components of the ubiquitin ligase complex (*see, e.g.,* the specification at page 4, lines 25-28). In particular, FBP5 was identified in a yeast 2-hybrid screen for it's ability to interact with Skp1 (*see, e.g.,* the specification at page 72, line 1 to page 78, line 28). Sequence analysis of the nucleic acid encoding FBP5 (SEQ ID NO: 9) revealed the presence of an F-box motif and immunoprecipitation experiments confirmed that FBP5 can interact with Skp1 (*see, e.g.,* the specification at page 78, lines 29 to 32; page 80, lines 1 to 9). Accordingly, the specification has provided further evidence that FBP5 is an F-box protein that does indeed interact with the components of the ubiquitin ligase complex. These teachings in the specification thus exceed the threshold requirement of specific utility and substantial utility. The Examiner alleges that the specification fails to teach any functional characterization of the claimed nucleic acid or protein encoded. As discussed above, since FBP5 was first identified based on its interaction with the components of the ubiquitin ligase complex, together with the identification of an F-box motif in the sequence, these characteristics indicate that the molecules of the present invention are subunits of ubiquitin ligase. Thus, the specification provides teachings that exceed the threshold requirement of specific utility.

A substantial utility, according to the Guidelines, is a utility that defines a "real world use" and an assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would define a "real world" context of use (see Office Action, page 5). As discussed previously, deregulation of FBPs is implicated in cancer development (*see, e.g.,* the specification at pages 3, line 3 to page 4, line 7; Amendment, filed June 1, 2007, page 6-7). The specification teaches that the nucleic acid molecules of the present invention can be used as probes for detecting FBP5. The specification also teaches that the FBP5 nucleic acid of the present invention is mapped and localized to chromosome position 6q25-26, a region shown to be a site of loss of heterozygosity in human ovarian, breast, and gastric cancer hepatocarcinomas, Burkitt's lymphomas, gliomas, and parathyroid adenomas (*see, e.g.,* the specification at page 56, lines 8 to 14). The specification on page 57, lines 8-25 further teaches that FBP5 can be detected by hybridization assays (e.g., Northern blots, in situ-hybridization). Translocations, deletions and point mutations of FBP5 can be detected by Southern blotting, FISH, RHLP analysis, SSCP, and PCR. The specification further teaches that the protein encoded by SEQ ID NO:9 may be used as an immunogen to generate antibodies which immunospecifically bind FBP5

(page 38, lines 10 to 32). These antibodies can be used to detect aberrant FBP5 localization or aberrant levels of FBP5 in a patient tissue or serum sample (page 56, lines 21 to 27). Accordingly, the claimed invention has a "real-world" or substantial utility.

In view of the foregoing remarks, the Examiner has not established a prima facie case for lack of specific and substantial utility and Applicants respectfully request that the rejection of claims 50-55 under 35 U.S.C. § 101 be withdrawn.

3. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner has maintained the rejection of claim 52 under 35 U.S.C. § 112, second paragraph for indefiniteness. The Examiner alleges that the term "highly stringent conditions" as recited in claim 52, is a relative term which renders the claim indefinite.

The Examiner alleges that the term "highly stringent conditions" is not defined in claim 52 and that one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Without making any admission as to the merits of the Examiner's rejection, Applicants have amended claim 52 to specify the highly stringent conditions for hybridization, wherein said highly stringent conditions comprise hybridization in 0.5M $NaHP0_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA at 65°C, and washing in of 0.1xSSC/0.1% SDS at 68°C. Support for the amendment to claim 52 can be found in the specification at *e.g.*, page 19, line 31 to page 20, line 7.

As such, Applicants submit that claim 52 is definite and that the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

4. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner had maintained the rejection of claims 52-55 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully disagree with the rejection for the reasons detailed below.

The factual inquiry of whether there is sufficient written description under 35 U.S.C. § 112 is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the invention as now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q. 2d 1111, 1117 (Fed. Cir. 1991). Disclosure of sufficiently detailed, relevant identifying characteristics, *i.e.*, structure, physical, and/or chemical properties, functional characteristics when coupled with a

known or disclosed correlation between function and structure, or combination of such characteristics can provide evidence that Applicant was in possession of the claimed invention. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d at 964, 63 U.S.P.Q.2d at 1613 (Fed. Cir. 2002).

Independent claim 52 relates to an isolated nucleic acid molecule comprising a nucleotide sequence derived from a mammalian genome that hybridizes under highly stringent conditions to the complement of nucleotide sequence of SEQ ID NO: 9; and encodes a gene product which contains an F-box motif and binds to Skp1, wherein said highly stringent conditions comprise hybridization in a buffer consisting of 0.5M $NaHP0_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C.

The Examiner alleges that the specification has not disclosed the sequences of any DNA sequences of mammals that hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9 and encodes a gene product which contains an F-box motif and binds to Skp1. In particular, the Examiner alleges that the specification fails to describe what DNA molecules fall into the claimed genus because there is no definition of "highly stringent conditions" (see Office Action, page 14). As discussed above, amended claim 52 sets forth the highly stringent conditions for hybridization, which are fully supported by the specification (*see, e.g.*, page 19, line 31 to page 20, line 2). As such, one skilled in the art would readily be able to distinguish those DNA molecules that fall within the claimed genus from those that do not by performing hybridization under the highly stringent conditions set forth in claim 52. The methods for performing hybridization are well known in the art at the time the application was filed (*see, e.g.,* Ausubel *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. 1, Green Publishing Associates, Inc., and John Wiley & Son, Inc., New York, at p. 2.10.3).

It would be clear to one skilled in the art that not all sequences that hybridize to the complement of SEQ ID NO:9 are encompassed by the claims – only those that contain an F-box motif and bind to Skp1. The Examiner alleges that the specification does not describe any assays to analyze whether a nucleotide sequence encodes a gene product which contains an F-box motif and binds to Skp1, as recited in claim 52 (see Office Action, page 14). Applicants respectfully direct the Examiner's attention to the specification at page 7, lines 1-5, which defines "F-box motif" as a stretch of approximately 40 amino acids that is necessary for the interaction of F-box containing proteins with Skp1. The specification teaches a Yeast Two-Hybrid Screening for detecting F-box proteins that bind to Skp1 (*see, e.g.*, the

specification at page 72, line 19 to page 74, line 3; page 78, lines 15 to 28). BLAST programs, available through the National Center for Biotechnology Information and The Institute for Genomic Research, were used to identify F-box motifs in the cDNA clones identified via Yeast Two-Hybrid Screening (*see, e.g.*, the specification at page 74, lines 25 to 33; page 78, lines 28 to 32). The specification also teaches several assays to confirm the specificity of interaction between the FBPs identified via Yeast Two-Hybrid Screening and human Skp1. Translated FLAG-tagged FBPs were tested for binding to His-tagged Skp1 pre-bound to Nickel-agarose beads (*see, e.g.*, the specification at page 75, lines 10 to 18; page 80, lines 1 to 9). The specification also teaches an *in vivo* assay for determining the interaction of a candidate FBP with Skp 1, wherein FLAG-tagged FBP is expressed in Hela cells from which cell extracts are made and subjected to immunoprecipitation with an anti-FLAG antibody (*see, e.g.*, the specification at page 80, lines 15 to 23). Skp1 is then detected in an immunoblot with a specific antibody to Skp1 (*see, e.g.*, the specification at page 80, lines 15 to 23). Thus, the specification teaches binding assays for an F-box protein and Skp1. Accordingly, the specification conveys to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

As discussed in the previously filed Amendment, in Example 9 of the Synopsis of Application of Written Description Guidelines, the specification discloses a single cDNA that encodes a protein of a particular function and a stringent hybridization was performed and several nucleic acids that encode proteins that perform the same function were isolated. (http://www.uspto.gov/web/patents/guides.htm; "Application Guidelines"). It is stated in the Application Guidelines that a person of skill in the art would not expect substantial variation among species because the hybridization conditions would set forth structurally similar cDNAs. Similarly in the present invention, a skilled artisan would not expect substantial variation among the species because the hybridization conditions as set forth in claim 52 would yield structurally similar FBP5 proteins. Thus, as in Example 9 of the Application Guidelines, a skilled artisan would reasonably conclude that the inventor had possession of the claimed invention, since stringent hybridization conditions for FBP5 are provided and the claims recite functional characteristics of the nucleic acid molecules of the invention that can be assayed for by one skilled in the art. Since there are high levels of skills and knowledge in the art of molecular biology, one skilled in the art would reasonably conclude that Applicants are in possession of the claimed invention.

Applicants respectfully submit that the requirement of written description is met and respectfully request that the rejection of claims 52-55 under 35 U.S.C. 112, first paragraph, be withdrawn.

Applicants further submit that new claim 76 also satisfies the written description requirement. New claim 76 relates to an isolated nucleic acid molecule comprising a nucleotide sequence which encodes a polypeptide comprising an amino acid sequence which has at least about 95% similarity to SEQ ID NO: 10 and binds to Skp1. Applicants submit that that one skilled in the art would be well aware of and able to employ in a straightforward manner standard methods that are routinely performed and well known in the art to determine that a nucleic acid molecule encodes a polypeptide comprising an amino acid sequence which has at least about 95% similarity to SEQ ID NO: 10. Furthermore, as discussed above on page 13 of this paper, the specification teaches several binding assays for an F-box protein and Skp1. Accordingly, the specification conveys to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention, as recited in new claim 76.

5. CLAIM REJECTIONS UNDER 35 U.S.C. § 102

The Examiner rejected claims 51-55 under 35 § U.S.C. 102(b) as allegedly being anticipated by Skowyra et al. (Cell, 1997, 91(2): 209-19; "Skowyra"). In response, Applicant respectfully submits that Skowyra fails to anticipate the claims for the reasons detailed below.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628 (Fed. Cir. 1987).

Skowyra fails to anticipate independent claim 51 or its dependent claims 53 to 55 because Skowyra does not teach each and every element of the claims. Specifically, Skowyra does not teach an isolated nucleic acid molecule comprising a nucleotide sequence that is at least 25 consecutive nucleotides of SEQ ID NO: 9, which encodes an F-box polypeptide, or a fragment thereof, as recited in claim 51. The Examiner alleges that any fragment of the nucleotide sequence of SEQ ID NO: 9, including the initiation codon, would be encompassed by claim 51. However, in order to anticipate amended claim 51, a nucleic acid molecule must encode an F-box polypeptide and must comprise a nucleotide sequence that is at least 25 consecutive nucleotides of SEQ ID NO: 9. Thus, the mere presence of an ATG in a nucleic acid sequence that encodes an F-box polypeptide is not sufficient to anticipate the

claims. Moreover, sequence alignments of SEQ ID NO: 9 with yeast Cdc4 cDNA and yeast Grr1 cDNA were performed using the LALIGN program which finds the best local alignments between SEQ ID NO:9 and yeast Cdc4 cDNA; and between SEQ ID NO:9 and yeast Grrl cDNA are less than 25 consecutive nucleotides in length (Exhibit A). Thus, the nucleotide sequences of yeast Cdc4 and yeast Grr1 do not comprise a nucleotide sequence of SEQ ID NO: 9 that is at least 25 nucleotides in length nor would they hybridize under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9. Similarly, new claim 75 teaches an isolated nucleic acid molecule comprising a nucleotide sequence that is at least 25 consecutive nucleotides from nucleotide position 1 to nucleotide position 1409 of SEQ ID NO:9, Skowyra does not anticipate the invention in new claim 75.

Skowyra fails to anticipate independent claim 52 or its dependent claims 53 to 55 because Skowyra does not teach each and every element of the claims. Skowyra does not teach an isolated nucleic acid molecule derived from a mammalian genome comprising a nucleotide sequence that hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9 and encodes a gene product which contains an F-box motif and binds to Skp1, as recited in claim 52. Skowyra discloses Cdc4 cDNA and Grr1 cDNA, both of which encode yeast F-box proteins that bind to Skp1. Since nucleic acid molecules that encode yeast proteins are not derived from a mammalian genome, Skowyra does not anticipate the invention in claim 52. The Examiner further alleges that the coding sequences corresponding to the F-box motif present in the Cdc4 and Grr1 would hybridize under stringent conditions to the nucleotide sequence of SEQ ID NO: 9, as required by claim 52. As discussed above, since there is no sequence homology between SEQ ID NO:9 and yeast Cdc4 or between SEQ ID NO:9 and yeast Grrl, the coding sequences corresponding to the F-box motif present in the Cdc4 and Grrl would not hybridize under stringent conditions to the nucleotide sequence of SEQ ID NO:9. Thus, Skowyra does not anticipate independent claim 52 or its dependent claims 53 to 55. Similarly, Skowyra does not anticipate new claim 76. Since yeast Cdc4 and yeast Grrl are not homologous to SEQ ID NO:9, Skowyra certainly does not anticipate an isolated nucleic acid molecule that comprises a nucleotide sequence which encodes a polypeptide comprising an amino acid sequence which has at least about 95% similarity to SEQ ID NO:10.

Accordingly, Applicants respectfully submit that the Skowyra does not teach each and every element of claims 51 to 55 and as such, the rejection under 35 § U.S.C. 102(b) should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the formal objections have been obviated and rejections to the pending claims should be withdrawn. Applicants respectfully submit that all claims are now in condition for allowance. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

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